

## **II. REMARKS**

Upon entry of the present amendment, claims 1 to 4, 6 to 11, 16 to 37, 39 to 63, 65, 66, 68, 69, and 72 to 75 will be pending. Claims 18, 30, and 58 have been withdrawn from consideration, but remain pending.

### **A. Regarding the Amendments**

Claims 5, 12 to 15, 38, 64, 70 and 71 and, pursuant to the restriction requirement, claim 67, are cancelled herein without disclaimer, and without prejudice to Applicants' pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application.

Claim 1, and the claims in general, have been amended to clarify that the subject matter of the invention is directed to "sets" of primers and primer pairs, which together allow primer extension and amplification, respectively, of the entire authentic PKD1 gene, but not of PKD1 homologs. The amendment is supported, for example, at paragraph 45 (page 22) and, therefore, does not add new matter.

Claim 1 also has been amended to incorporate the language of previously pending claim 5, which has been cancelled herein. As such, it is submitted that the amendment does not add new matter.

Claim 1 also has been amended to clarify that the selective hybridization is that which occurs under "highly stringent conditions." The amendment is supported, for example, at paragraph 56 (page 28) and, therefore, does not add new matter.

In addition, claim 1 has been amended to state that a primer of the set hybridizes to a flanking region of "one" of the specified PKD1 gene sequences. The amendment merely makes clear that one primer of the set is specific to one of the recited regions and, therefore, that the set includes at least eight primers, one of each is which is specific for one of each of the recited PKD1 regions. As such, the amendment does not introduce new matter.

Claims 7, 63, and 65 have been amended to a dependent form. The amendments merely clarify the claimed subject matter by referring to previous claims that are directed to the subject matter previously recited in claims 7, 63 and 65. As such, the amendments do not add new matter.

Claim 16, which previously depended from claim 5 (now cancelled), has been amended to depend from claim 1, which now recites the language of previously pending claim 5. As such, the amendment merely addresses a formality, and does not add new matter.

The claims depending from claim 1, or claims depending therefrom (e.g., claim 7), have been amended generally to refer to the "set" of primers (claim 1) or primer pairs (claim 7). The amendment is necessitated by the amendments to claim 1 and claim 7, and merely addresses a formality. As such, it is submitted that the amendment does not add new matter.

The claims also have been amended generally to delete the term "about", except that the term is maintained in claim 7 because the scope of the subject matter encompassed within the term is defined by claim 1, from which claim 7 depends, and which requires that the primers hybridize within 50 nucleotides of the specified sequences. It is submitted that the deletion of the term "about" merely clarifies the subject matter of the invention, and does not add new matter.

**B. Regarding the Election/Restrictions**

Pursuant to the Restriction Requirement mailed May 23, 2002, claim 67 has been cancelled as directed to a non-elected invention.

With respect to the species election, Applicants note that the claims directed to the non-elected subject matter has been maintained. It is noted that the various non-elected species are now encompassed within the amended claims. As such, Applicants respectfully request that, if the presently claimed generic subject matter (e.g., claim 1) is deemed allowable, the Examiner reconsider and rejoin the non-elected species, which depend from and, therefore, contain the limitations of the generic and any intervening claims.

**C. Prior Art Rejections**

The rejection of claims 1 to 7, 20 to 22, 24, 31, 37 to 39, 43, 44, 46 to 49, 59, and 62 under 35 U.S.C. § 103(a) as allegedly anticipated by Klinger et al. (U.S. Pat. No. 5,654,170) is respectfully traversed.

It is stated in the Office Action that Klinger et al. describe a primer that meets the requirements of the claims in Figure 3B (see, also, col. 5, line 45, to col. 6, line 4), and that, while the reference does not teach that the Figure 3 primer can be extended, the reference describes authentic PKD1 and homolog sequences, and primers to preferentially amplify the authentic sequence, alone. As such, it is alleged that it would have been obvious to practice the teaching of Klinger et al. to obtain primers capable of differentiating PKD1 from a homolog because the reference states that a detailed comparison of the authentic and homolog sequences enables the design of such primers.

The primers of the claimed set of primers are characterized, in part, in have a 5' region that selectively hybridizes to authentic PKD1 and, optionally, a PKD1 homolog, and a 3' region that selectively hybridizes to PKD1, but not to a PKD1 homolog sequence. As such, the primers encompassed within the invention allow, for example, the amplification of authentic PKD1 gene sequences, but not PKD1 homologs.

As was discussed in the Interview, the sequence of the homolog shown above the spaces (:::) of the authentic PKD1 sequence includes a duplicated region of authentic PKD1 (indicated by wavy lines over the homolog and under the authentic PKD1 in the attached copy of Fig. 3A; Exhibit A), and, as pointed out by the Examiners, a region that diverges from the authentic sequence (indicated by a straight underline in Exhibit A). The position corresponding to the Fig. 3B oligonucleotide is indicated by parentheses in Exhibit A.

Referring to the attached copy of Fig. 3 (Exhibit A), Applicants point out that the 5' region of the Fig. 3B oligonucleotide corresponds to the “divergent” (underlined) region of the homolog, and that this portion of the oligonucleotide (AGGACCTGT) is not present in the authentic PKD1 sequence (see sequence 3' to wavy underlined portion of authentic PKD1). As such, the 5' region of the Fig. 3B oligonucleotide would be expected to selectively hybridize to the PKD1 homolog, but not likely to authentic PKD1. Further, the 3' region of the Fig. 3B oligonucleotide is identical to sequences of both authentic PKD1 and the homolog and, therefore, would hybridize to both. Thus, in direct contrast to the claimed primers, the Fig. 3B oligonucleotide contains a 5' region that hybridizes to a PKD1 homolog, but not likely to authentic PKD1, and a 3' region that hybridizes to both authentic PKD1 and the homolog. As such, the Fig. 3B oligonucleotide does not teach or suggest a primer that can be used to amplify authentic PKD1, but not a homolog.

As mentioned above, the Examiners noted that inspection of Fig. 3A of Klinger et al. revealed that the homolog sequence in the duplicated region diverges from corresponding “authentic” sequence (see underlined sequence in Exhibit A, Fig. 3A), and, therefore, may provide information that would allow for the preparation of a primer as claimed. Applicants submit, however, that Fig. 3A of Klinger et al. does not provide the information required to teach a primer encompassed within the claimed sets of primers. Specifically, the claims require that a primer of the invention includes a 3’ region that selectively hybridizes to PKD1, but not to a PKD1 homolog and, therefore, knowledge of a sequence that is present in authentic PKD1, but not in a homolog.

Fig. 3A of Klinger et al. do not teach or suggest a sequence of authentic PKD1 that is not present in the homolog sequence but, instead, describe sequences that are present in the homolog, but not in authentic PKD1. For example, referring to Exhibit A, Klinger et al. show an “A” (circled; Fig. 3A) in the homolog that is not represented in the authentic PKD1 (see boxed “G” in corresponding position of authentic). However, this information does not, in turn, teach a “G” that is present in authentic PKD1 but not the homolog because, in fact, the homolog contains a nucleotide sequence that corresponds to the “boxed” G in the authentic PKD1 (i.e., directly above the boxed G in Exhibit A, Fig. 3A). As such, Fig. 3A, at best, provides information to make a primer that contains a 3’ region that selectively hybridizes to the PKD1 homolog (e.g., the circled A), but not to authentic PKD1. However, Fig. 3A does not provide any sequence of authentic PKD1 that is not present in the homolog sequence shown and, therefore, cannot teach or suggest a primer that having a “3’ region that selectively hybridizes to a PKD1 gene sequence, and not to a PKD1 gene homolog sequence” as recited in the claims.

For the above reasons, it is submitted that Klinger et al. do not teach or suggest the set of primers as set forth in claim 1 because the reference does not provide any examples of such primers or regions of PKD1 from which such primers could be made, and does not provide any specific information that would allow one of ordinary skill to have a reasonable expectation of successfully making such primers. Accordingly, it is submitted that Klinger et al. would not have rendered the subject matter of claim 1 obvious or, therefore, the subject matter of claims 2 to 4, 6, 7, 25, 31, 37, 39, 43, 44, 46 to 49, and 59, each of depends directly or indirectly from claim 1 (e.g., via claim 7). With respect to the rejections of claim 5 and 38, it is noted that these claims has been cancelled and, therefore, the rejection is moot.

With respect to the rejections of claims 20 to 22 and 62, it is stated that Klinger et al. describe the claimed subject matter, wherein the contiguous nucleotide sequence comprises a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted (i.e., the elected species), and further teaches that deletions may be detected by PCR (col. 8, lines 36-40). Applicants submit, however, that the disclosure of the PKD1 sequence in Klinger et al. and a general statement in the reference stating that "deletions may be detected" does not provide sufficient specificity such that one of ordinary skill in the art would have had a reasonable expectation of identifying the specified deletion (or other mutations as set forth in claim 20). Accordingly, since Klinger et al. do not appear to refer specifically to any of the claimed polynucleotides and, for the reasons described above, do not appear to provide the primers that would allow the identification of such mutations, it is submitted that Klinger et al. would not have rendered obvious the subject matter of claim 20 or, therefore, claims 21, 22, or 62, each of which depends from claim 20.

In summary, Klinger et al. do not teach or suggest the claimed sets of primers or primer pairs, or the claimed mutant PKD1 sequences, and do not provide sufficient teaching such that

one of ordinary skill in the art would have had a reasonable expectation of making such primers. Accordingly, it is submitted that the Klinger et al. reference would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejections of the claims under 35 U.S.C. § 103(a) be removed.

The rejection of claims 16, 17, 19, and 40 to 42 under 35 U.S.C. § 103(a) as allegedly obvious over Klinger et al. in view of Stefano is respectfully traversed.

Klinger et al. is provided as discussed above. Stefano et al. is provided as describing high density arrays of nucleotides and high throughput DNA analysis, including performing such analysis on solid supports. As such, it is alleged that it would have been obvious to combine the references to obtain the claimed subject matter because of the advantage of reduced cost and labor by applying the high throughput methods, and the benefit of identifying the presence of unknown mutations.

Applicants submit, however, for the reasons set forth above, that Klinger et al. do not teach or suggest a set of primers as claimed or, therefore, compositions comprising such primers or methods of using the primers. Stefano similarly does not teach a set of primers as claimed and, therefore, does not provide the teaching missing in Klinger et al. As such, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claims 16, 17, 19, and 40 to 42 as allegedly obvious over Klinger et al. in view of Stefano be removed.

The rejection of claims 8 to 15, 26, 28, 29, 54, 68 to 72 and 74 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al. is respectfully traversed. It is noted that claims 12 to 15 have been canceled.

Klinger et al. is applied as discussed above. It is stated in the Office Action that Klinger et al. do not teach the primers set forth as SEQ ID NOS:3, 4, 19 and 20, only the sequence in the genomic form of SEQ ID NO:1. It is stated that it would have been obvious to one of ordinary skill in the art to select the primers set forth as SEQ ID NOS:3, 4 19, and 20 from the PKD1 sequence of Klinger et al. for the expected benefit of obtaining functionally equivalent primers with the ability to selectively prevent the amplification of PKD1 homologue sequences. In this manner authentic PKD1 sequences are selectively amplified (Col. 5 lines 64-67). In support of the rejection, it is stated that Buck teaches that any of various different primers are functionally equivalent and, citing to *In re Deuel*, which states that "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties...", alleged that the claimed primers merely represent structural homologs that can be derived from the sequences suggested by the prior art as useful for detecting PKD1, but not PKD1 homologs.

As discussed above, however, Klinger et al. merely provide a vague description of oligonucleotides that one may be able to identify, but do not providing any teaching or suggestion of sufficient specificity such that one of ordinary skill would have had a reasonable expectation of obtaining a set of primers or primer pairs as claimed. Buck similarly does not describe with any specificity oligonucleotides useful as primer pairs for amplifying the specified portions of PKD1 as recited in the claims and, therefore, does not provide the teaching that is missing from Klinger et al. As such, it is submitted that the cited references, whether considered alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, is respectfully requested that the rejection of claims 8 to 15, 26, 28, 29, 54, 68 to 72 and 74 as unpatentable over Klinger et al. in view of Buck et al. be removed.



The rejection of claims 27, 53, 55, 60, 61, 73 and 75 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. is respectfully traversed.

Klinger et al. and Buck et al. are applied as discussed above. It is stated in the Office Action that Klinger et al. and Buck et al. do not describe the nesting of primers, but that Shapira et al. describe amplifying nucleic acids using nested PCR. As such, it is alleged that it would have been obvious to combine the cited references to obtain the benefits provided by nested PCR.

Applicants point out that claims 27, 53, 55, 60, 61, 73 and 75 ultimately depend from claim 7, which depends from claim 1. For the reasons set forth above, it is submitted that Klinger et al. and Buck et al., either alone or in combination, do not teach or suggest the primers of claim 1 or, therefore, the primer pairs of claim 7 and, therefore, do not teach or suggest methods of using the primer pairs. Shapira et al. do not teach or suggest the primers of claim 1, or primer pairs that can amplify the portions of PKD1 as recited in claim 7, and, therefore, do not provide the teaching that is missing in Klinger et al. and Buck et al. Accordingly, it is respectfully requested that the rejection of claims 27, 53, 55, 60, 61, 73 and 75 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. be removed.

The rejection of claims 32, 33, 35 and 36 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Sathe et al. is respectfully traversed.

Klinger et al. and Buck et al. are applied as discussed above. It is stated in the Office Action that Klinger et al. and Buck et al. do not describe using temperature melting HPLC or SSCP analysis on an amplification product to detect a mutation, but that Sathe et al. describe detecting mutations using such methods. As such, it is alleged that it would have been obvious

to combine the cited references to obtain the benefits of the techniques of Sathe et al. as a viable alternative to direct sequencing to detect mutation.

Applicants point out that claims 32, 33, 35 and 36 ultimately depend from claim 7, which depends from claim 1. For the reasons set forth above, it is submitted that Klinger et al. and Buck et al., either alone or in combination, do not teach or suggest the primers of claim 1 or, therefore, the primer pairs of claim 7 and, therefore, do not teach or suggest methods of using the primer pairs. Sathe et al. do not teach or suggest the primers of claim 1, or primer pairs that can amplify the portions of PKD1 as recited in claim 7, and, therefore, do not provide the teaching that is missing in Klinger et al. and Buck et al. Accordingly, it is respectfully requested that the rejection of claims 32, 33, 35 and 36 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Sathe et al. be removed.

The rejection of claims 50 to 52 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Iliff is respectfully traversed.

Klinger et al. is applied as discussed above. It is stated that Klinger et al. do not teach or suggest transmitting a report via internet fax, or mail, but that Iliff describes a disease management system that provides such options to patients as a means of receiving information such as a summary of a consultation session. It is stated that it would have been obvious to combine the teachings of the cited references for the expected benefit of promoting patient health in a cost effective manner.

Applicants point out that claims 50 to 52 ultimately depend from claim 7, which depends from claim 1. For the reasons set forth above, it is submitted that Klinger et al. do not teach or suggest the primers of claim 1, or the primer pairs of claim 7, and, therefore, do not teach or suggest methods of using the primer pairs as required of claims 50 to 52. Iliff et al. do not teach or suggest primers as set forth in claim 1, or primer pairs that can amplify the portions of PKD1 as recited in claim 7, and, therefore, do not provide the teaching that is missing in Klinger et al.

Accordingly, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claims 50 to 52 as unpatentable over Klinger et al. in view of Iliff be removed.

The rejection of claims 55 to 57 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. and of Sathe et al. is respectfully traversed.

Klinger et al., Buck et al., and Shapira et al. are applied as discussed above. It is stated in the Office Action that Klinger et al., Buck et al., and Shapira et al. do not describe using temperature melting HPLC or SSCP analysis on an amplification product to detect a mutation, but that Sathe et al. describe detecting mutations using such methods. As such, it is alleged that it would have been obvious to combine the cited references to obtain the benefits of the techniques of Sathe et al. as a viable alternative to direct sequencing for mutation detection.

Applicants point out that claims 55 to 57 ultimately depend from claim 7, which depends from claim 1. For the reasons set forth above, it is submitted that Klinger et al., Buck et al., and Shapira et al., either alone or in combination, do not teach or suggest the primers of claim 1, or the primer pairs of claim 7, and, therefore, do not teach or suggest methods of using the primer pairs. Sathe et al. also do not teach or suggest the primers of claim 1, or primer pairs that can amplify the portions of PKD1 as recited in claim 7, and, therefore, do not provide the teaching that is missing in Klinger et al., Buck et al., and Shapira et al. Accordingly, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claims 55 to 57 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. and of Sathe et al. be removed.

The rejection of claims 63 to 66 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Ahern et al. is respectfully traversed. It is noted that claim 64 has been canceled.

Klinger et al. is applied as discussed above. It is stated in the Office Action that Klinger et al. do not describe a kit for detecting the presence or absence of a mutation in PKD1, but that Ahern et al. teach that kits offer scientists a good return on investment by providing required reagents. As such, it is alleged that it would have been obvious to combine the cited references for the benefit of convenience and to save time.

As amended, claims 63 depends from claim 1 and claim 65 depends from claim 7. The kits of claim 66 contain polynucleotides, which are defined the same as the polynucleotides of claim 20. For the reasons set forth above, Klinger et al. do not describe such primers, primer pairs, or polynucleotides. Ahern et al. similarly do not teach or suggest such primers, primer pairs, or polynucleotides and, therefore, do not provide the teaching that is missing in Klinger et al. Accordingly it is submitted that the cited references, either alone or in combination, would not have rendered the claimed kits obvious and, therefore, respectfully requested that the rejection of claims 63, 65 and 66 as unpatentable over Klinger et al. in view of Ahern et al. be removed.

The rejection of claim 34 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Koster et al. is respectfully traversed.

Klinger et al. and Buck et al. are applied as discussed above. It is stated in the Office Action that Klinger et al. and Buck et al. do not describe the use of MALDI-TOF mass spectrometry to detect the presence or absence of a mutation in an amplification product, but that Koster et al. teach that MALDI-TOF can be used to sequence nucleic acids by analysis of nested fragments. As such, it is alleged that it would have been obvious to combine the cited references for the benefit of obtaining a high speed, high throughput method.

Applicants point out that each of the rejected claims ultimately depend from claim 7, which depends from claim 1, and, as discussed above, Klinger et al. but do not teach or suggest the primers of claim 1 or, therefore, the primer pairs of claim 7, particularly not the primer pairs set forth as SEQ ID NOS:3 and 4 and SEQ ID NOS:19 and 20, and that Buck similarly does not describe with any specificity oligonucleotides useful as primer pairs for amplifying the specified portions of PKD1 as recited in the claims. Koster et al. also do not teach or suggest such primers or primer pairs and, therefore, do not provide the teaching missing in Klinger et al. and Buck et al. Accordingly, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claim 34 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Koster et al. be removed.

#### **E. Rejections under 35 U.S.C. § 112**

The objection to the specification and corresponding rejection of claims 1 to 66 and 68 to 75 under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description are respectfully traversed.

It is stated that the claims encompass a variety of primers, primer pairs, and polynucleotides, but that claim 7 as written, for example, could encompass any T3 or T7 primer pair that "can amplify" a cloned region of SEQ ID NO:1 comprising about nucleotides 2043 to 4290. It is stated that the instant claims encompass nucleic acids and methods that comprise any number of potential sequences when one considers that they encompass nucleic acids that comprise partial matches to the recited SEQ ID numbers and the ability to hybridize to and can amplify even more sequences. As such, it is alleged that the claims encompass any number of possible primers comprising any number of known and unknown nucleic acid fragments, but that the specification only discloses SEQ ID NO:1 and primers of SEQ ID NOS:3, 4, 19 and 20. It is further alleged that "...the sequence of nucleotides of SEQ ID NO:1 and all aforementioned

variations, are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision...." (*Id.*)

Claim 1 has been amended to clarify that a primer of the claimed set of primers selectively hybridizes under highly stringent conditions to a nucleotide sequence within 50 nucleotides of one of the specified sequences of SEQ ID NO:1 (e.g., within 50 nucleotides of nucleotides 2043 to 4290 of SEQ ID NO:1). Applicants submit that the specification provides (and claims recite) a sufficient structural and functional description of the claimed subject matter such that the skilled artisan would have known that Applicants were in possession of the full scope of the claimed subject matter.

With respect to the structural definition of the claimed subject matter, Applicants point out that the specification discloses the full length PKD1 gene sequence (SEQ ID NO:1), and the authentic PKD1 gene sequences of interest (i.e., the nucleotide sequences as recited in claim 1). Further, the specification discloses an exemplary set of primers (and primer pairs) specific for the eight PKD1 gene regions as recited in claim 1 (e.g., SEQ ID NOS:3 and 4 allow amplification of nucleotides 2043 to 4290 of SEQ ID NO:1, but not of a PKD1 homolog; see, also, Table 1, page 103).

With respect to the functional definition of the claimed subject matter, Applicants point out that each primer of the claimed set is defined by the ability of the 3' region of the primer to selectively hybridize to a PKD1 gene sequence, but not to a PKD1 homolog. This functional requirement further defines a primer of the invention in that the 3' region comprises a sequence that is present in an authentic PKD1 gene, but not in a homolog, such that extension of the primer in the presence of a polymerase only occurs when the primer is hybridized to authentic PKD1. The specification discloses aligning SEQ ID NO:1 with PKD1 homologs to identify such

regions (see, e.g., paragraphs 223-225 (pages 101-102), and further discloses highly stringent hybridization conditions that allow for the required selective hybridization of the 3' region of a probe to PKD1 but a homolog (see, e.g., paragraph 61, pages 30-31; see, also, Table 1, page 103, disclosing an annealing temperature ( $T_m$ ) for the exemplified primers, and paragraph 227, providing the conditions).

In view of the above-described structural and functional characteristics of the primers of the invention as set forth in the specification, it is submitted that one skilled in the art, viewing the subject application, would have known that Applicants were in possession of the full scope of the claimed subject matter. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, first paragraph under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

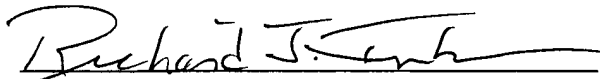
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The Commissioner is hereby authorized to charge any other fees that may be associated with this communication, or credit any overpayment, to Deposit Account No. 07-1896.

Respectfully submitted,

Date: November 23, 2004

  
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